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(54) Title: ERODIBLE POLYMERS FOR INJECTION

(57) Abstract: A composition for administration of a beneficial agent, contains a solvent mixture including a hydrophobic solvent and a hydrophilic solvent; a bioerodible polymer; and a beneficial agent. The polymer and the beneficial agent are dissolved. The composition has a low viscosity, allowing for easy injection through standard hypodermic needles.

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## ERODIBLE POLYMERS FOR INJECTION

### BACKGROUND

Controlled delivery of beneficial agents, especially peptide- and protein-based drug therapies, can be achieved through the use of bioerodible polymeric implants. Traditionally, this technology has involved surgical implantation of a polymeric monolith containing a suspended beneficial agent. Examples of these monoliths are described in U.S. patent nos. 6,110,503, 6,051,259, and 6,146,662. Certain complex shapes and/or formulations of these monoliths have been developed to provide specific rates of release of the beneficial agent over a period of time. A drawback to this implantation approach is the need to perform an incision in the patient in order to place the implant.

In order to eliminate the need for surgical implantation, implants have been developed which can be administered by the injection of a viscous composition. Compositions for injection must have a sufficient ability to flow so that the implant can pass through a syringe and needle. However, these formulations should not simply dissipate into the body but rather should form a discrete depot from which the drug is released. Typically, the composition transforms into a solid or a gel upon encountering the aqueous environment within an organism.

To accomplish this balance of physical properties, various formulations of bioerodible polymers, biocompatible solvents, beneficial agents, and other ingredients have been employed. Release of the beneficial agent from the polymeric matrix of the implant can then occur by: diffusion of the agent from the matrix; by degradation of the polymer and subsequent release of the agent into the surrounding environment; or by a combination of these two mechanisms.

One approach to the formulation of injectable compositions has been the use of solvents which are miscible or dispersible with water (hydrophilic solvents). For example, U.S. patent no. 6,143,314 describes injectable compositions containing poly(lactic acid-co-glycolic acid) (PLGA) and a

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hydrophilic solvent such as dimethyl sulfoxide (DMSO) or N-methyl pyrrolidone (NMP). U.S. patent nos. 5,278,201 and 4,938,763 describe poly(lactic acid), poly(glycolic acid), and their copolymers combined with NMP and a beneficial agent to form injectable liquid compositions. Depots of these same polymers also can be formed by injecting a composition containing a prepolymer, which then forms the polymer during the implantation process. As described in U.S. patent nos. 5,340,849 and 5,278,202, compositions of NMP, a beneficial agent, and polymer precursors can form a polymer gel upon injection into an aqueous environment due to polymerization of the polymer precursors in the presence of water.

The beneficial agent can be either dissolved or dispersed in these formulations. Water-soluble beneficial agents, including peptides and proteins, are typically dissolved by the solvents which are miscible in aqueous body fluids. The solvents used in these compositions tend to provide for the rapid influx of water into the implant. This promotes rapid solidification of the polymer at the implant site and promotes diffusion of the beneficial agent from the implant, often resulting in an initial, rapid release of the beneficial agent. This "burst" often results in the release of a substantial portion of the beneficial agent within a very short time. For example, 25-75% of the beneficial agent can be released within 24 hours of administration. In some cases, the burst can be followed by a drastic reduction in the release of the beneficial agent before a gradual release begins. This pause in the release behavior is referred to as a "lag time."

A burst effect and/or lag time can be unacceptable, particularly in circumstances where sustained delivery is desired. For example, it may be desirable to deliver the beneficial agent over a period of a week or a month or longer. To control release rates of these systems, it is often necessary to include additional ingredients which can moderate the release of the beneficial agent and/or control the porosity of the implant. For example, U.S. patent nos. 5,599,552 and 5,487,897 describe complex compositions which use poly(D,L-lactic acid) to provide an implant that has a porous or liquid core surrounded by a layer, or "skin," of polymer. This morphology is reported to

provide for a more uniform release rate. Release of a beneficial agent can also be controlled by complexing the agent to make it less soluble in water, as described in U.S. patent no. 5,780,044; however, complexation can affect the activity, and thus the efficacy, of the beneficial agent.

5 An alternative approach to the formulation of controlled release compositions has been the use of solvents which are immiscible with water. For example, U.S. patent no. 6,130,200 describes gels of PLGA and a water-immiscible (hydrophobic) solvent in which peptide-based drugs are suspended as particles. When administered, the gels have sufficient  
10 dimensional stability to form a cohesive depot. The hydrophobic solvent in these systems inhibits the rapid uptake of water, resulting in the reduction or elimination of any burst release. One drawback to this system is the high viscosities exhibited by the gels. Large diameter needles (16-gauge to 20-gauge) must be employed to administer the composition by injection, and high  
15 pressures are necessary for administration. This can be especially disadvantageous in the treatment of chronic conditions, such as the administration of insulin to diabetic patients. Another drawback is the tendency of the particulate beneficial agent to settle out of the composition over time. This instability can necessitate special storage conditions, short  
20 storage times, and/or special handling conditions during administration. If the beneficial agent settles out once the implant is in the organism, the rate of release of the agent over time can become unpredictable.

25           There is thus a need for compositions for the gradual release of a beneficial agent which can be easily administered by injection. These compositions will ideally exhibit controlled release of the agent, without unintended periods of rapid release or zero release. Additionally, stability for long periods of time and under various storage conditions would be desirable.

## BRIEF SUMMARY

30 In a first aspect, the present invention is a composition for administration of a beneficial agent, containing: a solvent mixture including a

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hydrophobic solvent and a hydrophilic solvent; a bioerodible polymer; and a beneficial agent. The polymer and the beneficial agent are dissolved.

5 In a second aspect, the present invention is a composition for administration of a beneficial agent, containing: a solvent mixture including a hydrophobic solvent and a hydrophilic solvent; a bioerodible polymer; and a beneficial agent. The viscosity of the composition is less than 2000 centipoise.

10 In a third aspect, the present invention is a composition for administration of a beneficial agent, containing: a solvent mixture including a hydrophobic solvent and a hydrophilic solvent; a bioerodible polymer dissolved in the solvent mixture; and a beneficial agent dissolved in the solvent mixture. The viscosity of the composition is less than 2000 centipoise, at least 90 wt% of the solvent mixture is the hydrophobic solvent, the hydrophobic solvent has a solubility in water of less than 0.1 wt%, and less  
15 than 5% of the beneficial agent is released in 24 hours following administration *in vivo*.

In a fourth aspect, the present invention is a method of administering a beneficial agent, including injecting the above compositions into an organism through a needle.

20 In a fifth aspect, the present invention is a kit containing a container; a hydrophobic solvent; a hydrophilic solvent; a bioerodible polymer; and a beneficial agent. The amount of the hydrophobic solvent and the hydrophilic solvent is sufficient together to dissolve all of the polymer and the beneficial agent.

## 25 BRIEF DESCRIPTION OF THE DRAWINGS

Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood from the following detailed description when considered in connection with the accompanying drawings in which like reference  
30 characters designate like or corresponding parts throughout the several views and wherein:

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Figure 1 is a view of a vial containing an injectable composition.

Figures 2-4 are graphs illustrating the release of rhGH over time.

Figure 5 is a graph illustrating the release of VEGF over time.

5 Figure 6 is a graph illustrating the release of rhGH over time.

## DETAILED DESCRIPTION

The present invention includes a solution or emulsion of a bioerodible polymer dissolved in a mixed solvent system containing at least two solvents. The polymer solution or emulsion is mixed with a beneficial agent to form a  
10 liquid or gel which can be injected into an organism, preferably using a needle having a diameter no greater than that of a 20-gauge needle. The beneficial agent is then slowly released from the composition into the organism. Compositions can be prepared and administered to provide for continual release of a beneficial agent over a period of time with minimal burst release  
15 upon injection. The compositions of the invention are especially useful for peptide- and protein-based beneficial agents. The solution or emulsion of polymer in the solvent mixture preferably provides for stabilization of the beneficial agent during storage and during the release period.

The mixed solvent system dissolves both the polymer and the  
20 beneficial agent. Preferably, the composition is a solution, which means a liquid having multiple ingredients homogeneously distributed in a single phase. Alternatively, the composition may be an emulsion having more than one liquid phase. Both solutions and emulsions are contrasted with suspensions, which have a liquid phase containing a suspended solid phase.

25 It is preferred that the solvents in the solvent mixture exhibit different levels of solubility in water. The solvent which is less soluble in water is called the hydrophobic solvent, and the solvent which is more soluble in water is called the hydrophilic solvent.

30 Water solubility may be determined experimentally as follows: five grams of water are placed in a clear container at 20°C and weighed, and a solvent is added dropwise. The solution is swirled to observe phase

separation. When the saturation point appears to be reached, as determined by observation of phase separation, the solution is allowed to stand overnight and is checked again the following day. If the solution is still saturated, as determined by observation of phase separation, then the percent by weight of solvent added is determined. Otherwise more solvent is added and the process repeated. Solubility is determined by dividing the total weight of solvent added by the final weight of the solvent/water mixture.

Preferably the hydrophobic solvent accounts for more than half of the mass of the solvent mixture. Useful hydrophobic solvents exhibit a solubility in water less than 1 wt%, preferably less than 0.5 wt%, more preferably less than 0.1 wt%. Especially preferred are hydrophobic solvents having a solubility in water less than 0.05 wt%.

Examples of hydrophobic solvents include the alkyl and aralkyl esters of aryl acids such as benzoic acid, phthalic acid, and salicylic acid; alkyl esters of citric acid, such as triethyl citrate and tributyl citrate; aryl, aralkyl and alkyl ketones and aldehydes; and mixtures thereof. Among preferred solvents are those having solubilities within the foregoing range selected from (i) compounds having the structural formulas:  $R^1-C(=O)-O-R^2$  or  $R^1-C(=O)-R^2$  in which  $R^1$  is aryl or aralkyl,  $R^2$  is alkyl or aralkyl, and  $R^1$  and  $R^2$  are optionally the same or different, with the proviso that when each of  $R^1$  and  $R^2$  are alkyl, the total carbon atoms in  $R^1$  and  $R^2$  combined are 4 or more, (ii) alkyl and aralkyl esters of phthalic acid, isophthalic acid and terephthalic acid, and (iii) alkyl and aralkyl esters of citric acid. Alkyl means straight, branched, or cyclic hydrocarbons having preferably 1-20 carbon atoms, optionally substituted with non-interfering substituents. Aralkyl means (alkyl)phenyl, for example benzyl, phenethyl, 1-phenylpropyl, and 2-phenylpropyl. Aryl means phenyl, optionally substituted by non-interfering substituents. Many of the solvents useful in the invention are available commercially (SIGMA/ALDRICH, Milwaukee, WI) or may be prepared by conventional esterification of the respective arylalkanoic acids using acid halides, and optionally esterification catalysts, such as described in U.S. patent no. 5,556,905, and in the case of ketones and aldehydes, by oxidation of their respective alcohol precursors.

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Benzoic acid derivatives from which hydrophobic solvents may be selected include: 1,4-cyclohexane dimethanol dibenzoate, diethylene glycol dibenzoate, dipropylene glycol dibenzoate, polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol (200) dibenzoate, iso-decyl benzoate, neo-pentyl glycol dibenzoate, glyceryl tribenzoate, pentaerythritol tetrabenzoate, cumylphenyl benzoate, trimethyl pentanediol dibenzoate.

Phthalic acid derivatives from which hydrophobic solvents may be selected include: Alkyl benzyl phthalate, bis-cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate, diisooheptyl phthalate, butyl octylphthalate, diisononyl phthalate, nonyl undecylphthalate, dioctyl phthalate, diisooctylphthalate, dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear heptyl nonylphthalate, linear heptyl nonyl undecyl phthalate, linear nonyl phthalate, linear nonyl undecylphthalate, linear dinonyl didecylphthalate, diisodecyl phthalate, diundecyl phthalate, ditridecyl phthalate, undecyldodecyl phthalate, decyltridecyl phthalate, 1:1 blend of dioctyl and didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

Preferred hydrophobic solvents include the alkyl and aralkyl esters of the aryl acids described above. Examples of acids are benzoic acid and the phthalic acids, such as phthalic acid, isophthalic acid, and terephthalic acid. Most preferred solvents are derivatives of benzoic acid and include, for example, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, tert-butyl benzoate, isoamyl benzoate and benzyl benzoate, with benzyl benzoate being most especially preferred. Furthermore, mixtures of any of the hydrophobic solvents may also be used.

Hydrophilic solvents useful in solvent mixtures are those solvents that are miscible with the hydrophobic solvent and include, for example benzyl alcohol, methanol, 1-butanol, t-butanol, triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate,



triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glycerin, ethylene glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one, and mixtures thereof.

A useful hydrophilic solvent exhibits a solubility in water greater than the hydrophobic solvent with which it is mixed, typically between 1 wt% and up to and including miscibility with water, preferably up to and including 50 wt%, and most preferably up to and including 25 wt%. Especially preferred are hydrophilic solvents having a solubility in water from 2 wt% to 10 wt%.

The solvent mixture may contain more than two solvents. For example, the solvent mixture may contain two or more hydrophobic solvents, two or more hydrophilic solvents, and/or one or more solvents exhibiting a solubility in water which is between those of the specific hydrophilic and hydrophobic solvents. It is preferred that the total amount of solvent or solvents having a solubility in water of less than 1 wt% accounts for at least 55 wt% of the solvent mixture, preferably at least 75 wt% of the mixture, more preferably at least 90 wt% of the solvent mixture.

The polymers for use with the present invention are materials which decompose when placed inside an organism. Bioerodible polymers eliminate the need to remove the implant after the beneficial agent has been released, since the polymer will gradually break down and may be metabolized or excreted from the body. This decomposition can be observed as a decline in the molecular weight of the polymer over time. Polymer molecular weights can be determined by a variety of methods including size exclusion chromatography (SEC), and are generally expressed as weight averages or number averages. A polymer is bioerodible if, when in phosphate buffered saline (PBS) of pH 7.4 and a temperature of 37°C, its weight-average

molecular weight is reduced by at least 25% over a period of 6 months as measured by SEC.

Bioerodible polymers which are useful for the present invention include polyesters, such as poly(caprolactone), poly(glycolic acid), poly(lactic acid),  
5 and poly(hydroxybutyrate); polyanhydrides, such as poly(adipic anhydride) and poly(maleic anhydride); polydioxanone; polyamines; polyamides; polyurethanes; polyesteramides; polyorthoesters; polyacetals; polyketals; polycarbonates; polyorthocarbonates; polyphosphazenes; poly(malic acid); poly(amino acids); polyvinylpyrrolidone; poly(methyl vinyl ether); poly(alkylene  
10 oxalate); poly(alkylene succinate); polyhydroxycellulose; chitin; chitosan; and copolymers and mixtures thereof.

The beneficial agent can be any physiologically or pharmacologically active substance or substances optionally in combination with pharmaceutically acceptable carriers and additional ingredients such as  
15 antioxidants, stabilizing agents, etc. that do not substantially adversely affect the advantageous results that may be attained from administration of the beneficial agent. The beneficial agent may be any of the agents which are known to be delivered to the body of a human or an animal. These agents include drug agents, medicaments, vitamins, and nutrients. Included among  
20 the types of agents which meet this description are lower molecular weight compounds, proteins, peptides, genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility inhibitors and fertility promoters.

Drug agents which may be delivered by the present invention include drugs which act on the peripheral nerves, adrenergic receptors, cholinergic  
25 receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable  
30 agents may be selected from, for example, proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, polypeptides, steroids, analgesics, local anesthetics, antibiotic agents, anti-

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inflammatory corticosteroids, ocular drugs and synthetic analogs of these species.

Examples of drugs which may be delivered by the composition of the present invention include, prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, mecamlamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, theophylline choline, cephalixin hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl tetranitrate, digoxin, isofluorophate, acetazolamide, methazolamide, bendroflumethiazide, chloropromamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its derivatives such as betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17- $\alpha$ -hydroxyprogesterone acetate, 19-norprogesterone, norgestrel, norethindrone, norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyl dopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalixin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine,

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tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine.

Preferably, the beneficial agent is a protein or peptide, more preferably a heterologous glycoprotein. Examples of heterologous glycoproteins include

5 molecules such as cytokines and their receptors, as well as chimeric proteins comprising cytokines or their receptors, including, for example tumor necrosis factor alpha and beta, their receptors (TNFR-1; Gray et al., (1990) Proc. Natl. Acad. Sci. USA 87:7380-7384; and TNFR-2; Kohno et al., (1990) Proc. Natl. Acad. Sci. USA 87:8331-8335) and their derivatives; renin; growth hormones,

10 including human growth hormone, bovine growth hormone, methionine-human growth hormone, des-phenylalanine human growth hormone, and porcine growth hormone; growth hormone releasing factor (GRF); parathyroid and pituitary hormones; thyroid stimulating hormone; human pancreas hormone releasing factor; lipoproteins; colchicine; prolactin; corticotrophin; thyrotropic

15 hormone; oxytocin; vasopressin; somatostatin; lypressin; pancreozymin; leuprolide; alpha-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; luteinizing hormone releasing hormone (LHRH); LHRH agonists and antagonists; glucagon; clotting factors such as factor VIIIc, factor IX, tissue factor, and von

20 Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator other than a tissue-type plasminogen activator (t-PA), for example a urokinase; bombesin; thrombin; hemopoietic growth factor; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory

25 protein (MIP-1-alpha); a serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; chorionic gonadotropin; gonadotropin releasing hormone; bovine somatotropin; porcine somatotropin; a microbial protein, such as beta-lactamase; DNase; inhibin; activin; vascular

30 endothelial growth factor (VEGF); receptors for hormones or growth factors; integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3,

NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF- $\beta$ ; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-alpha and TGF-beta, including TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3, TGF- $\beta$ 4, or TGF- $\beta$ 5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD-3, CD-4, CD-8, and CD-19; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-alpha, -beta, -gamma, and consensus interferon; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; viral antigen such as, for example, a portion of the HIV-1 envelope glycoprotein, gp120, gp160 or fragments thereof; transport proteins; homing receptors; addressins; fertility inhibitors such as the prostaglandins; fertility promoters; regulatory proteins; antibodies and chimeric proteins, such as immunoadhesins; analogs and derivatives of these compounds, and pharmaceutically acceptable salts of these compounds, or their analogs or derivatives.

Beneficial agents can also include chemotherapeutic agents, specifically the local application of such agents to avoid or minimize systemic side effects. Compositions containing chemotherapeutic agents may be injected directly into the tumor tissue for sustained delivery of the chemotherapeutic agent over time. In some cases, particularly after resection of the tumor, the composition may be implanted directly into the resulting cavity or may be applied to the remaining tissue as a coating. Representative chemotherapeutic agents that may be delivered include, for example, carboplatin, cisplatin, paclitaxel, BCNU, vincristine, camptothecin, etoposide, cytokines, ribozymes, interferons, oligonucleotides and oligonucleotide sequences that inhibit translation or transcription of tumor genes, functional derivatives of the foregoing, and typically known chemotherapeutic agents such as those described in U.S. patent no. 5,651,986.

Further examples of beneficial agents include antibacterial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; anti-inflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamisole; immune reagents such as immunoglobulin or antigens; anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, and vitamin C; and antioxidants such as alphanatocopherol and butylated hydroxy toluene. The composition may also contain pharmaceutically acceptable carriers and additional ingredients, and these substances may be dissolved or may be suspended.

The beneficial agent, polymer, and solvent components may be mixed together in one step or may be mixed together in separate steps, in any order. It is preferred to dissolve the polymer in the mixed solvent, followed by dissolution of the beneficial agent. Some or all of the mixed solvent or a solvent component may be added to the polymer and/or the beneficial agent in order to solubilize the powder before the composition is mixed together. The various mixing steps can involve heating and/or mechanical mixing in order to form the homogeneous solution.

The amount of beneficial agent in the mixture is preferably equal to a unit dosage. A unit dosage is the amount of beneficial agent necessary to produce the desired beneficial effect in the organism to which it is administered. The absolute amount of a unit dosage can depend on many factors including, for example, the type of agent, the efficacy of the agent, the health of the organism, and the size of the organism.

The concentration of the beneficial agent can be varied, for example according to the amount of dosage required, the release rate, or the solubility of the beneficial agent. The concentration can be from 0.1 milligram per milliliter of solution (mg/ml) to 500 mg/ml, preferably from 5 mg/ml to 250 mg/ml, more preferably from 10 mg/ml to 100 mg/ml. It is preferred that the

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concentration of the beneficial agent is not so great that a portion of the beneficial agent separates into a separate phase from the solution.

Compositions as described may be administered in a variety of ways. Preferred methods of administration involve injection. Injection may be subcutaneous, parenteral, intramuscular, or other types of injection known to those skilled in the art. A consideration for administration by injection is the viscosity of the mixture. For example, the viscosity of the liquid should be sufficiently low to allow the mixture to be injected through a 20 gauge needle. Preferably the solution can be injected through a 25 gauge needle, more preferably through a 28 gauge needle, even more preferably through a 30 gauge needle. A composition can be injected through a needle when a pressure of 20 psig, applied to the plunger of an attached syringe, results in a flow of the composition of at least 1.0 milliliters/minute from the needle.

The viscosity of the liquid can be measured using a CANON-FENSKE viscometer at a temperature of 25°C. The kinematic viscosity of the liquid is preferably at most 2000 centipoise, including 2000-50 centipoise. Examples include less than 1600 centipoise, less than 1400 centipoise, less than 1200 centipoise, less than 1000 centipoise, less than 900 centipoise, less than 800 centipoise, less than 700 centipoise, less than 600 centipoise, less than 500 centipoise, less than 400 centipoise, less than 300 centipoise, less than 200 centipoise, less than 100 centipoise, and less than 50 centipoise, and all ranges therebetween.

For an implant administered by injection, the liquid mixture preferably transforms into a depot upon contact with the fluid in the body. This depot is characterized by its phase separation from the physiological fluid and its increased viscosity relative to the original liquid composition. It is this depot that serves as the polymeric implant for controlled release of the beneficial agent.

One possible mechanism for the release behavior of these compositions involves the phase separation of the beneficial agent within the implant upon administration. As the hydrophilic solvent diffuses into the aqueous surroundings, at least a portion of the beneficial agent separates into

a separate phase from the rest of the depot composition. This phase separation then results in a fine suspension of the beneficial agent within the depot. Release of the beneficial agent would then occur slowly and gradually, without an initial burst release or lag time.

5           When the composition is administered *in vivo*, preferably less than 5% of the beneficial agent is released from the depot in 24 hours, more preferably less than 2% of the beneficial agent is released from the depot in 24 hours, even more preferably less than 1% of the beneficial agent is released from the depot in 24 hours, even more preferably less than 0.05% of the beneficial agent is released from the depot in 24 hours, even more preferably less than 0.01% of the beneficial agent is released from the depot in 24 hours. The organism to which the composition is administered can be, for example, a rat or a human.

15           The release of the beneficial agent preferably occurs over a period of days, weeks, or months. It is preferred that at least 25% of the total amount of beneficial agent is released within one year of administration, more preferably at least 25% of the total amount of the beneficial agent is released within one month of administration, most preferably at least 25% of the total amount of the beneficial agent is released within one week of administration.

20           Alternatively, it is preferred that at least 20% of the total amount of beneficial agent is released within one year of administration, more preferably at least 20% of the total amount of the beneficial agent is released within one month of administration, most preferably at least 20% of the total amount of the beneficial agent is released within one week of administration. The desired

25           length of the release period will vary according to the physiological treatment desired.

30           The composition may be conveniently packaged in a sterile container, such as the vial 10 illustrated in Figure 1. This container may be part of a kit which may optionally contain a sterile syringe and needle. The vial 10 may be sealed with a septum 12. This septum seals the liquid 14 and may be pierced by a needle and syringe to permit withdrawal of the mixture. The vial may contain all the ingredients necessary for the controlled release of the



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beneficial agent. The liquid composition in the vial preferably contains a unit dosage of the beneficial agent. It is preferred that the end user of the mixture not be required to add further ingredients or to measure the dosage prior to administration. The liquid composition may be contained in a syringe such that it can be directly administered by injection.

Alternatively, the composition may be packaged in more than one container. For example, a solution of polymer in a solvent or solvent mixture may be in one vial, and a solution of the beneficial agent in a solvent or solvent mixture may be in another vial. The solvents and/or solvent mixture may be the same or different. The contents of the vials may be combined and mixed, and the final composition administered by injection. In another example, the beneficial agent and polymer may be in one container, and the solvent mixture may be in another container. The beneficial agent and polymer may be provided together as a powder, or the beneficial agent and polymer may be provided together as a tablet or capsule. The beneficial agent and polymer may be combined with the solvent mixture such that the polymer and beneficial agent dissolve, and the final composition administered by injection. In another example, the polymer may be provided as a solution in the solvent mixture in a vial, and the beneficial agent may be provided in a separate container. Alternatively, the beneficial agent may be provided as a solution in the solvent mixture in a vial, and the polymer may be provided in a separate container. The contents of the containers may be combined such that a liquid formulation is formed, and the final composition administered by injection.

Preferably, the packaging of the composition or its components is disposable, more preferably recyclable. It is preferred that the composition and its packaging are sterile.

## EXAMPLES

### Examples 1-5

In these examples, compositions containing protein were prepared such that they could be easily administered by injection, yet would provide for

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a gradual, controlled release of the protein. Release behaviors (release profile) of rhGH (GENENTECH, S. San Francisco, CA) from the compositions were studied both *in vivo* and *in vitro* by measuring the amount of protein released as a function of time. The stability of the protein was determined by measuring the percentage of the released protein which had not aggregated. A higher percentage of non-aggregated protein indicated better stability.

Poly(L-lactic acid) (PLA) was obtained from BOEHRINGER INGELHEIM, Ridgefield, CT, as RESOMER 202H, with a reported molecular weight of 12,000 daltons. Polymer solutions were prepared by mixing the benzyl alcohol and benzyl benzoate to form a homogenous mixture. PLA was then added to this mixture and was dissolved by gentle mixing with a vortex mixer. The rhGH was complexed with zinc (10 moles Zn/mole protein), and powders of the complexed protein, sucrose, and surfactant were prepared using a bench top spray dryer.

The relative amounts of ingredients used for making the protein powders and the polymer solutions are given in Tables 1 and 2 respectively. For Examples 1-4, the appropriate protein powder was dissolved in the polymer solution to give an overall concentration of 50 mg/ml of protein. For Example 5, the appropriate protein powder was dissolved in the polymer solution to give an overall concentration of 100 mg/ml of protein. Dissolution was accomplished by gentle mixing with a vortex mixer followed by homogenization at 8000 rpm for 2 minutes, using a 5-mm fine screen shear homogenizer to ensure a uniform solution. The resulting solutions could be injected through a 25-gauge needle.

Table 1

Protein Formulation	Concentrations (mg/mL)			Protein Content (wt%)
	Protein	Sucrose	Tween 20	
A	20.0	2.0	0.05	60.0
B	20.0	5.0	0.05	50.0

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Table 2

Example	Polymer Solution (wt %)			Protein Formulation	% Release in 24 hr	% Non-aggregated protein**
	PLA	Benzyl Alcohol	Benzyl Benzoate			
1	20	5	75	A*	3.8	99.6
2	20	5	75	B*	1.4	73.0
3	30	5	65	A*	--	--
4	30	5	65	B*	--	--
5	20	5	75	B***	0.6	85.5

\* Added to polymer solution at a concentration of 50 mg/mL

\*\* Determined by SEC-HPLC

\*\*\* Added to polymer solution at a concentration of 100 mg/mL

For *in vitro* release studies, 100 microliter ( $\mu$ L) samples of the resulting liquid were placed in 1.5 mL of release buffer and held at 37°C for 24 hours. The release buffer was 50 mM HEPES, 5 mM EDTA, 0.1mM  $\text{NaN}_3$ , with a pH of 8.0. The entire release medium was then analyzed by size exclusion chromatography - high performance liquid chromatography (SEC-HPLC) to determine total protein content and percentage of non-aggregated protein present, using a method similar to that described in Maa et. al., J. Pharm Sci. 2(87) 152-159, 1998. The SEC-HPLC was run using a 7.8 X 300 mm TSK 2000-SWXL column at room temperature, with a mobile phase of 50mM  $\text{NaH}_2\text{PO}_4$ , 150 mM NaCl, pH 7.2. The flow rate was 1.0 ml/min, and the run time was 20 min. Protein (10  $\mu$ g) was injected and the eluent monitored for absorbance at 214 nm. The results of *in vitro* release after 24 hours are given in Table 2.

Release profiles of the protein from the compositions *in vivo* were examined by pharmacokinetic studies. In these studies, SD rats were injected with a liquid composition at 5 milligrams protein/kilogram body weight (mg/kg) and 15 mg/kg. Injections were through 25-gauge needles. Serum samples were collected at the time of injection (time = 0 hr) and then at the time

intervals of 2, 4, 6, 8, 24, 96, and 168 hours. The serum samples were analyzed for rhGH by a specific rhGH ELISA (GENENTECH ASSAY SERVICES), having an assay detection limit of 0.1 nanograms per milliliter (ng/mL), to determine the concentration of rhGH in each sample. This protein concentration is due to the release of the protein from the implant. The resulting graphs of protein release over time are illustrated in Figures 2-4 for Examples 1, 3, and 4.

A comparative graph of Examples 1 and 5 is illustrated in Figure 6. In Example 1, a rapid rise in serum rhGH level was observed, and this was followed by a gradual decline to a plateau of 9 ng/mL after 4 days. In Example 5, a rapid rise in serum rhGH level was followed by a rapid decline to a plateau of 20 ng/mL after 24 hours. The pharmacokinetic data for these examples are given in Table 3.

Table 3

Example	Protein Formulation	rhGH Levels in Serum		
		Maximum (ng/mL)	Average 0-2 days (ng* day/mL)	Average 0-7 days (ng* day/mL)
1	A (50 mg/mL)	172.1	123.3	163.9
5	B (100 mg/mL)	249.0	64.5	163.1

#### Example 6

In this example, an injectable composition for controlled release of a protein was prepared. Release profiles of the protein from the composition were studied both *in vivo* and *in vitro* by measuring the amount of protein released as a function of time.

An aqueous protein solution was prepared by mixing VEGF (10 mg/ml), sucrose (10 mg/ml), 0.03% POLYSORBATE 80, and histidine (10 mM). The solution had a pH of 6.0. This protein solution was sprayed into liquid nitrogen using an ultrasonic nebulizer, as described in U.S. pat. no. 5,019,400. The resulting frozen protein droplets were then lyophilized to

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produce particles having a diameter of 2-10  $\mu\text{m}$ . The protein powder was mixed into a polymer solution composed of 30 wt% PLA, 69 wt% benzyl benzoate, and 1 wt% benzyl alcohol. The mixture was made into an emulsion by homogenization at 8,000 rpm for 2 minutes. The resulting mixture  
5 contained 12 mg protein per milliliter of liquid.

For *ex vivo* release studies, 100 microliter ( $\mu\text{l}$ ) samples were injected into 1.5 ml of a release buffer and held at 37°C. The release buffer was an aqueous mixture having a pH of 7.0, containing 10 mM histidine, 140 mM NaCl, 0.02% POLYSORBATE 20, and 0.02% sodium azide. At given  
10 intervals of time, the entire release medium was replaced with fresh buffer, the medium was then analyzed by SEC-HPLC to determine total protein content. The SEC-HPLC was run using a 7.8 X 300 mm TSK 300-SW column, having 5  $\mu\text{m}$  particles, at room temperature. The mobile phase was 25 mM  $\text{NaH}_2\text{PO}_4$ , 1.0 M NaCl with a pH of 7.4. The flow rate was 1.0 mL/min,  
15 and the run time was 20 min. Protein (25  $\mu\text{g}$ ) was injected and the eluent monitored for absorbance at 214 nm.

After 24 hours at 37°C, approximately 0.2% of the VEGF had been released. After an additional 168 hours, approximately 0.1% more of the VEGF was released.

The release profile of the protein from the composition *in vivo* was examined by pharmacokinetic studies. In this study, SD rats weighing between 265g and 302g were injected with a liquid composition at 3.6 mg/kg (dose volume of 0.3 ml/kg). Injections were through 25-gauge needles. Whole blood was collected from the rats in EDTA-treated microtainers and  
20 plasma harvested. The plasma samples were frozen until analysis and were then assayed using a VEGF ELISA to determine the concentration of VEGF in each sample. This protein concentration is due to the release of the protein from the implant. The resulting graph of protein release over time is illustrated in Figure 5. The initial plasma levels of rhVEGF were above 100 nanograms  
25 per milliliter (ng/ml) until 24 hours, after which the level remained around 100 picograms per milliliter (pg/ml) until 168 hours.  
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Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

## CLAIMS

1. A composition for administration of a beneficial agent to an organism, comprising:
  - a solvent mixture, comprising
    - a hydrophobic solvent; and
    - a hydrophilic solvent;
  - a bioerodible polymer; and
  - a beneficial agent,wherein the polymer and the beneficial agent are dissolved.
2. The composition of claim 1, wherein at least 55 wt% of the solvent mixture is the hydrophobic solvent.
3. The composition of claim 1, wherein at least 90 wt% of the solvent mixture is the hydrophobic solvent.
4. The composition of claim 1, wherein the hydrophobic solvent has a solubility in water of less than 0.1 wt%.
5. The composition of claim 1, wherein the beneficial agent has a concentration from 0.1 mg/ml to 500 mg/ml.
6. The composition of claim 1, wherein the beneficial agent has a concentration from 10 mg/ml to 100 mg/ml.
7. The composition of claim 1, wherein the composition can be injected through a 25-gauge needle.
8. The composition of claim 1, wherein the viscosity of the composition is less than 2000 centipoise.
9. The composition of claim 1, wherein less than 5% of the beneficial agent is released in 24 hours following administration *in vivo*.

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10. The composition of claim 1, wherein the hydrophobic solvent is benzyl benzoate, the hydrophilic solvent is benzyl alcohol, the bioerodible polymer is polylactide, and the beneficial agent is a peptide or protein.

5 11. The composition of claim 1, wherein the hydrophilic solvent, the hydrophobic solvent, the bioerodible polymer, and the beneficial agent form a homogeneous solution.

12. The composition of claim 1, wherein the hydrophilic solvent, the hydrophobic solvent, the bioerodible polymer, and the beneficial agent form an emulsion.

10 13. A composition for administration of a beneficial agent, comprising:  
a solvent mixture, comprising  
a hydrophobic solvent; and  
a hydrophilic solvent;  
15 a bioerodible polymer; and  
a beneficial agent,  
wherein the viscosity of the composition is less than 2000 centipoise.

20 14. The composition of claim 13 wherein at least 55 wt% of the solvent mixture is the hydrophobic solvent.

15. The composition of claim 13, wherein at least 90 wt% of the solvent mixture is the hydrophobic solvent.

16. The composition of claim 13, wherein the hydrophobic solvent has a solubility in water of less than 0.1 wt%.

25 17. The composition of claim 13, wherein the composition can be injected through a 28-gauge needle.



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18. The composition of claim 13, wherein the composition can be injected through a 30-gauge needle.

19. The composition of claim 13, wherein the viscosity of the composition is less than 500 centipoise.

5           20. The composition of claim 13, wherein the hydrophobic solvent is benzyl benzoate, the hydrophilic solvent is benzyl alcohol, the bioerodible polymer is polylactide, and the beneficial agent is a peptide or protein.

10           21. The composition of claim 13, wherein the hydrophilic solvent, the hydrophobic solvent, the bioerodible polymer, and the beneficial agent form a homogeneous solution.

22. The composition of claim 13, wherein the hydrophilic solvent, the hydrophobic solvent, the bioerodible polymer, and the beneficial agent form an emulsion.

15           23. A composition for administration of a beneficial agent to an organism, comprising:  
            a solvent mixture, the solvent mixture comprising a hydrophobic solvent and a hydrophilic solvent;  
            a bioerodible polymer dissolved in the solvent mixture; and  
            a beneficial agent dissolved in the solvent mixture,  
20           wherein the viscosity of the composition is less than 2000 centipoise, at least 90 wt% of the solvent mixture is the hydrophobic solvent, the hydrophobic solvent has a solubility in water of less than 0.1 wt%, and less than 5% of the beneficial agent is released in 24 hours following administration *in vivo*.

25           24. The composition of claim 23, wherein the hydrophobic solvent is benzyl benzoate, the hydrophilic solvent is benzyl alcohol, the bioerodible polymer is polylactide, and the beneficial agent is a peptide or protein.

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25. A method of administering a beneficial agent, comprising:  
injecting the composition of claim 1 into an organism through a needle.

26. The method of claim 25, wherein the needle is a 25-gauge  
needle.

5 27. The method of claim 25, wherein the needle is a 28-gauge  
needle.

28. The method of claim 25, wherein the needle is a 30-gauge  
needle.

10 29. A method of administering a beneficial agent, comprising:  
injecting the composition of claim 13 into an organism through a needle.

30. The method of claim 29, wherein the needle is a 25-gauge  
needle.

31. The method of claim 29, wherein the needle is a 28-gauge  
needle.

15 32. The method of claim 29, wherein the needle is a 30-gauge  
needle.

33. A method of administering a beneficial agent, comprising:  
injecting the composition of claim 23 into an organism through a needle.

20 34. A kit, comprising:  
a container;  
a hydrophobic solvent;  
a hydrophilic solvent;  
a bioerodible polymer; and  
a beneficial agent,  
25 wherein the amount of said hydrophobic solvent and said  
hydrophilic solvent is sufficient together to dissolve all of said polymer and  
said beneficial agent.

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35. The kit of claim 34, comprising a unit dosage of the beneficial agent.

36. The kit of claim 34, wherein the hydrophobic solvent, the hydrophilic solvent, and the bioerodible polymer are sterile.

5

37. The kit of claim 34, further comprising a syringe.

38. The kit of claim 34, wherein the container comprises a septum.

Figure 1

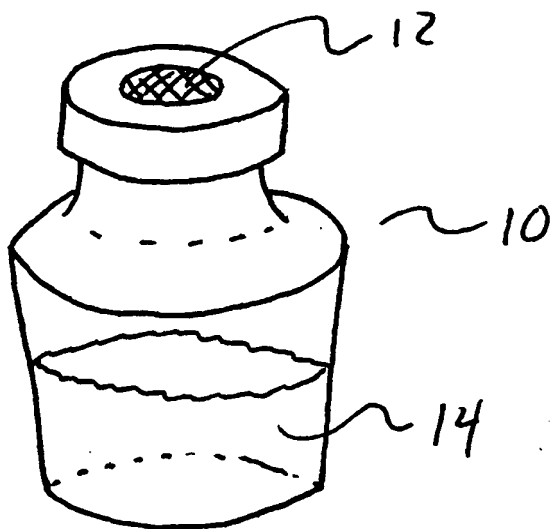


Figure 2

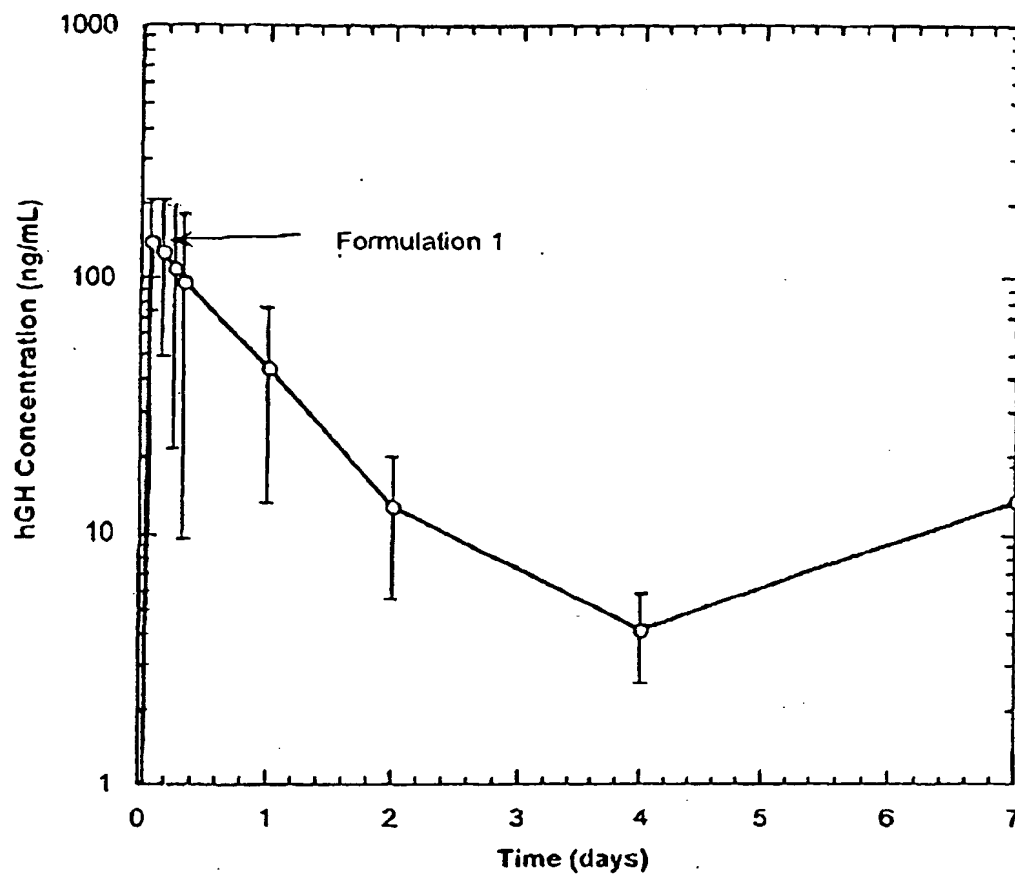


Figure 3

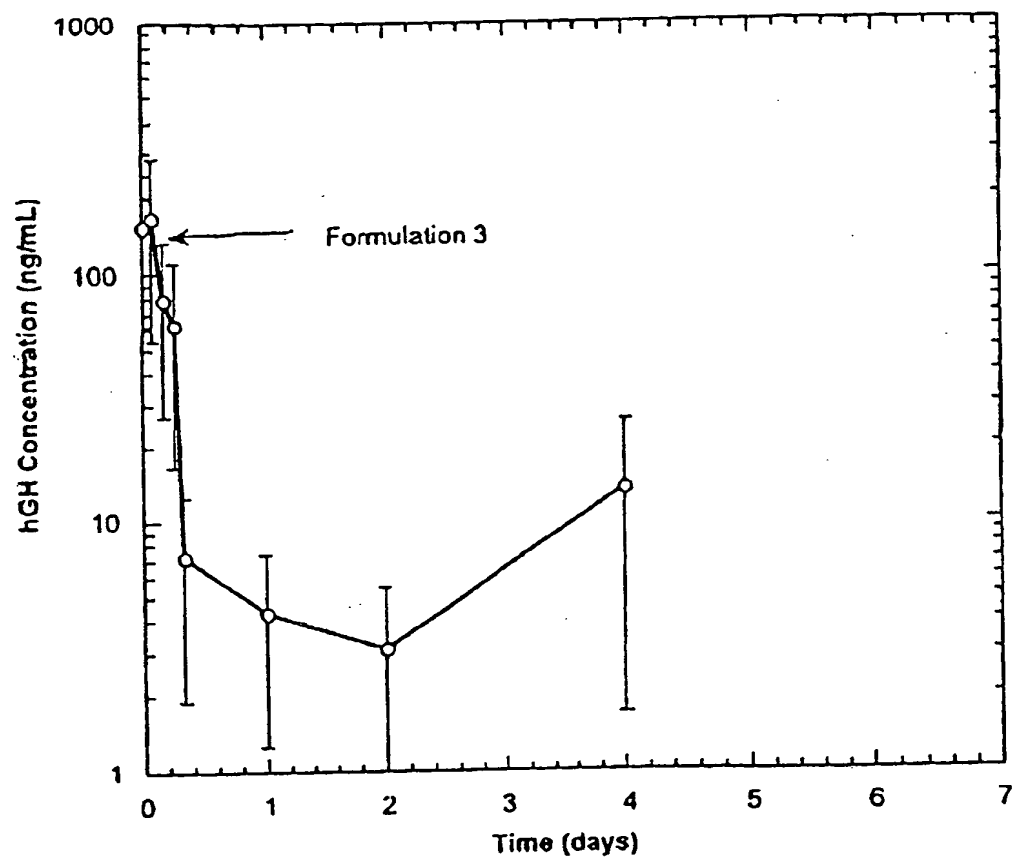


Figure 4

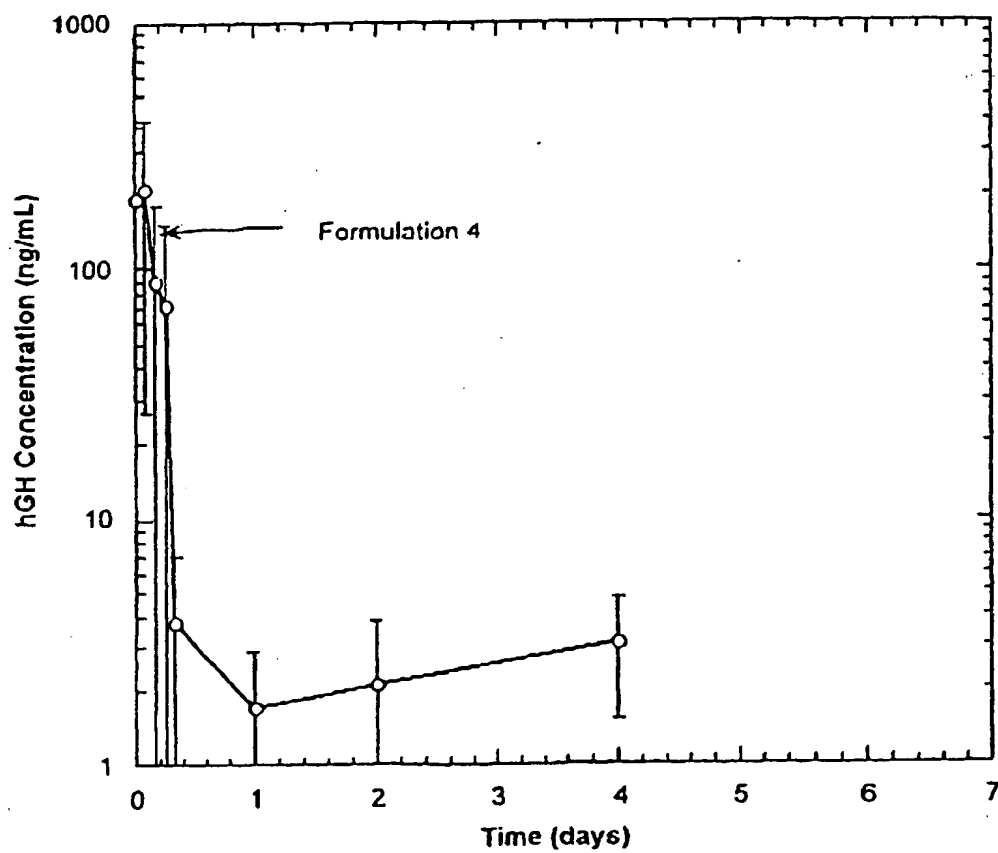


Figure 5

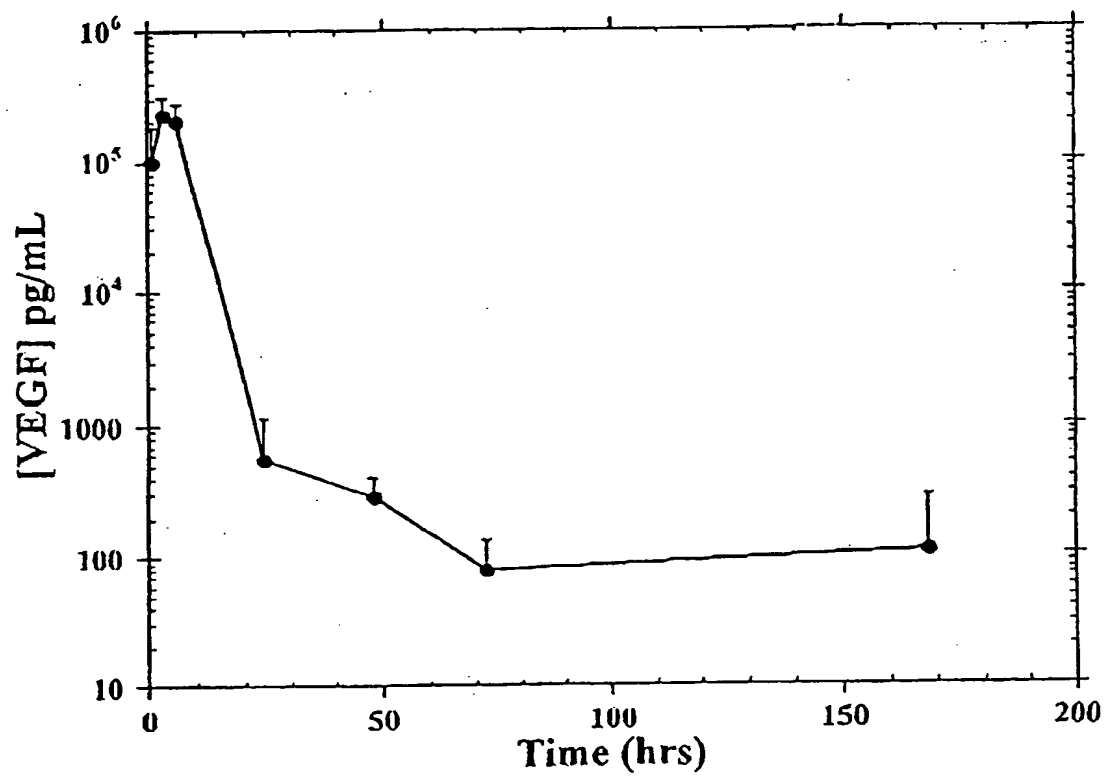
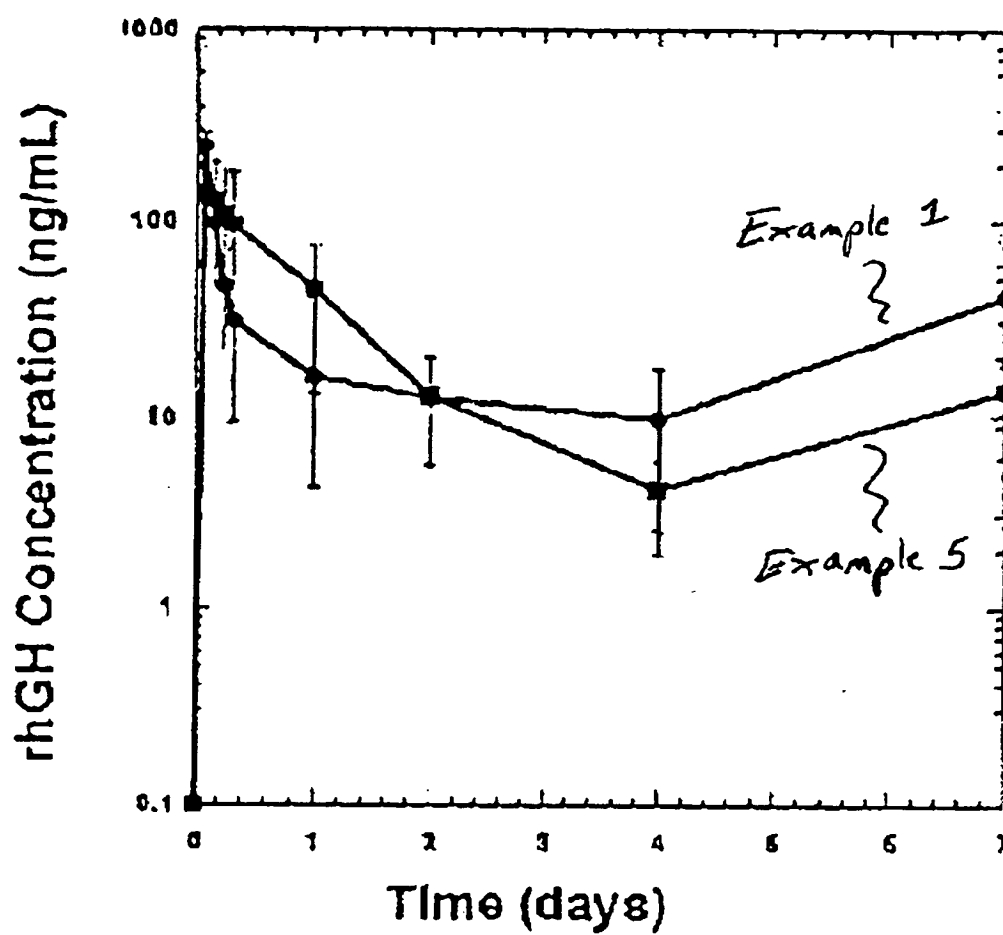




Figure 6



## INTERNATIONAL SEARCH REPORT

Int l Application No  
PCT/US 02/05445

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/12 A61K47/14 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 26015 A (DELAB) 24 July 1997 (1997-07-24)  claims 1,5,8,9,11 page 1, line 19 - line 27 page 3, line 17 -page 4, line 4 page 6; example 3 -----	1-9, 11-19, 21-23, 25-38

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

14 August 2002

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22/08/2002

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/05445

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9726015	A	24-07-1997	US 5980945 A	09-11-1999
			AU 1206497 A	11-08-1997
			CA 2242986 A1	24-07-1997
			EP 0874642 A1	04-11-1998
			WO 9726015 A1	24-07-1997
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